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Transannular Nitrone Cycloaddition. A Stereocontrolled Entry to the Spirocyclic Core of Pinnaic Acid

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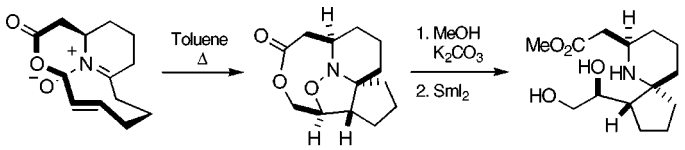
ABSTRACT



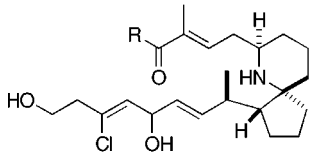
18 19 20

Thermolysis of lactone 18 initiated a stereospecific transannular nitrone−olefin [3 + 2] cycloaddition to yield tetracycle 19. Methanolysis followed by reductive cleavage of the isoxazolidine yielded 20, representing the azaspirocyclic core of pinnaic acid (1).

A cycloaddition in which the pair of addends are tethered to each other at *both* termini represents a special class of intramolecular reaction that offers unique advantages for synthesis. If the ring formed by connecting the addends in this manner is conformationally constrained, a predictable stereochemical outcome from the process of transannular cycloaddition should be possible in principle. This is not always the case in conventional intramolecular cycloadditions where only one tether links the two addends.

By far the best studied examples of transannular cycloaddition are transannular Diels−Alder (TADA) reactions.[1] Deslongchamps has demonstrated the practical value of TADA for the elaboration of complex polycyclic systems with a high degree of stereocontrol from relatively simple precursors.[2] However, aside from a few other examples involving [2 + 2] photoaddition,[3] transannular cycloadditions are a largely unexplored class of reactions.

We now report the first transannular nitrone cycloaddition (TANCA) where both dipole and dipolarophile are within a ring and show that it can proceed with a high degree of stereoselectivity.[4] We further demonstrate its applicability to a stereocontrolled synthesis of the azaspirocyclic core of the alkaloid family which includes pinnaic acid (**1**) and tauropinnaic acid (**2**).[5,6] In related studies directed toward the azaspirocyclic core of **1**, the conventional intramolecular nitrone cycloaddition chemistry of Grigg[7] gave isoxazolidines of incorrect relative configuration.[6e,f]



1, R = OH
2, R = $NH(CH_2)_2SO_3H$

(1) For a review, see: Deslongchamps, P. *Pure Appl. Chem.* **1992**, *64*, 1831.

(2) For some recent examples, see: (a) Marsault, E.; Deslongchamps, P. *Org. Lett.* **2000**, *2*, 3317. (b) Toro, A.; L'Heureux, A.; Deslongchamps, P. *Org, Lett.* **2000**, *2*, 2737. (c) Lavoie, R.; Ouellet, S. G.; Dallaire, C.; Dory, Y. L.; Toro, A.; Deslongchamps, P. *Tetrahedron* **2000**, *56*, 5509. (d) Frank, S. A.; Works, A. B.; Roush, W. R. *Can. J. Chem.* **2000**, *78*, 757. (e) Toro, A.; Nowak, P.; Deslongchamps, P. *J. Am. Chem. Soc.* **2000**, *122*, 4526.

(3) For a recent example, see: White, J. D.; Kim, J.; Drapela, N. E. *J. Am. Chem. Soc.* **2000**, *122*, 8665.

(4) Transannular nitrone cycloadditions in which the nitrone is external to the ring have been reported: (a) Baggiolini, E. G.; Lee, H. L.; Pizzolato, G.; Uskokovic, M.*J. Am. Chem. Soc.* **1982**, *104*, 6460. (b) Mihailovic, M. L.; Rajkovic, M. M.; Lorenc, L. B.; Pavlovic, V. D.; Milovanovic, A. Z.; Tinant, B.; Declercq, J.-P. *Tetrahedron* **1996**, *52*, 11995.

(5) Chou, T.; Kuramoto, M.; Otani, Y.; Shikano, M.; Yazawa, K.; Uemura, D. *Tetrahedron Lett.* **1996**, *37*, 3871.

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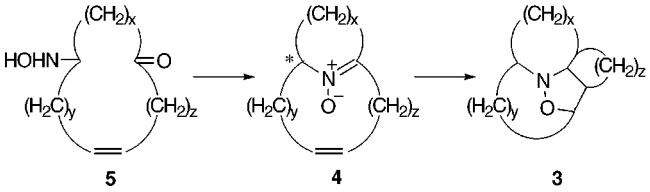
A generalized representation of our TANCA strategy is shown in Scheme 1, where a tetracyclic ($x \neq 0$) isoxazolidine

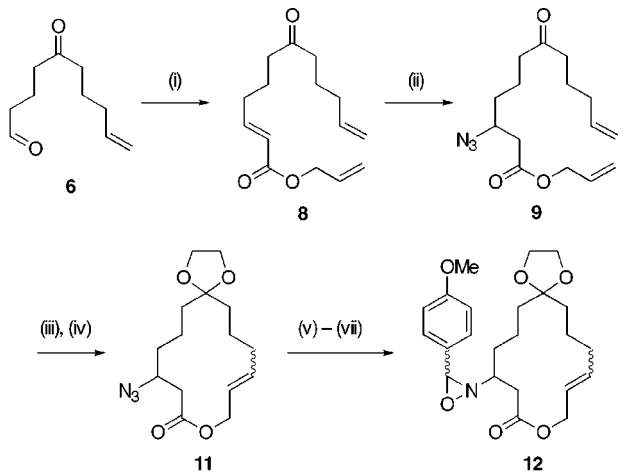
Scheme 1. Transannular Nitrone−Olefin Cycloaddition



3 bearing three new stereocenters is produced from nitrone **4**. The latter is itself prepared from transannular condensation of a hydroxylamine and a ketone function in **5**. An important requirement for stereocontrol in this reaction is that y and z must be large enough to permit flexibility in the approach of the nitrone to its olefin partner, but not so large as to allow the nitrone oxygen to pass through the plane of the macrocycle. If these conditions are met, the face of the alkene to which the nitrone adds will be determined by the single stereocenter (*) in **4** and hence by the configuration of the hydroxylamine in **5**. A system designed to test this concept was constructed using ring-closing metathesis[8] to produce a 14-membered macrocycle. A hydroxylamine and a ketone, both generated in situ, are positioned for transannular condensation to give the nitrone precursor for TANCA.

5-Oxo-9-decenal (**6**), prepared in four steps from cyclopentanone,[9] was subjected to a Wittig reaction with phosphoranylidene **7** to give the trans allylic ester **8** as the sole stereoisomer (Scheme 2). Conjugate addition of hydrazoic acid to **8** in the presence of triethylamine[10] afforded azide **9**

Scheme 2. Synthesis of Nitrone Precursor **12**

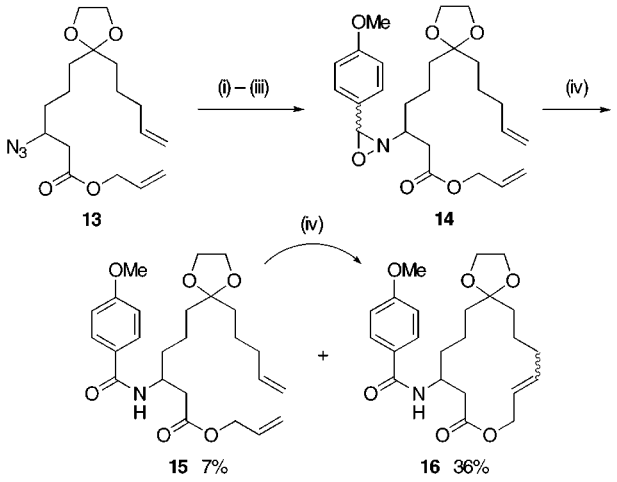


(i) $Ph_3PCHCO_2CH_2CH{=}CH_2$ (**7**), CH_2Cl_2, rt, 83%; (ii) HN_3, Et_3N, C_6H_6, Δ, 85%; (iii) $(CH_2OTMS)_2$, TMSOTf, CH_2Cl_2, −78 °C, 99%; (iv) $PhCHRuCl_2(PCy_3)_2$ (**10**), CH_2Cl_2, rt, 21%; (v) PPh_3, THF, *p*-$MeOC_6H_4CHO$, Δ; (vii) *m*-CPBA, CH_2Cl_2, −78 °C → rt, 79% from **11**.

which was converted to its ethylene ketal prior to ring-closing metathesis (RCM) with 20 mol % of Grubbs' catalyst **10**.[11] Deleterious side reactions presumably involving the azido moiety resulted in only a low yield of tridecanolide **11** which was obtained as an inseparable mixture of alkene isomers (E:Z = 4:1).[12] Staudinger reaction[13] of the azide **11** followed by aza-Wittig condensation of the resultant iminophosphorane with *p*-anisaldehyde yielded an imine which underwent selective oxidation with *m*-chloroperoxybenzoic acid (*m*-CPBA) to furnish oxaziridine **12**.[14] Diastereomers of the oxaziridine moiety (dr = 3:2) could be separated by column chromatography, but subsequent chemistry made this unnecessary.

In an attempt to improve the efficiency of the RCM of **9**, azide **13** was converted to oxaziridine **14** (dr = 1:1) before ring closure (Scheme 3). However, treatment of **14** with 10

Scheme 3. RCM of Oxaziridine **14**



(i) PPh_3, THF, Δ; (ii) *p*-$MeOC_6H_4CHO$, Δ; (iii) *m*-CPBA, CH_2Cl_2, −78 °C → rt, 44% from **13**; (iv) $PhCHRuCl_2(PCy_3)_2$ (**10**), CH_2Cl_2, rt.

mol % of catalyst **10** gave only the allyl dodecanoate **15** and the tridecanolide **16** (E:Z = 4:1) in 7% and 36% yields,

(6) For alternative approaches to the azaspirocyclic core of pinnaic acid, see: (a) Arimoto, H.; Asano, S.; Uemura, D. *Tetrahedron Lett.* **1999**, *40*, 3583. (b) Koviach, J. L.; Forsyth, C. J. *Tetrahedron Lett.* **1999**, *40*, 8529. (c) Clive, D. L. J.; Yeh, V. S. C. *Tetrahedron Lett.* **1999**, *40*, 8503. (d) Trauner, D.; Schwarz, J. B.; Danishefsky, S. J. *Angew. Chem., Int. Ed.* **1999**, *38*, 3542. (e) Lee, S.; Zhao, Z. *Tetrahedron Lett.* **1999**, *40*, 7921. (f) Shindo, M.; Fukuda, Y.; Shishido, K. *Tetrahedron Lett.* **2000**, *41*, 929. (g) Wright, D. L.; Schulte, J. P.; Page, M. A. *Org. Lett.* **2000**, *2*, 1847.

(7) Grigg, R.; Markandu, J.; Surendrakumar, S.; Thornton-Pett, M.; Warnock, W. J. *Tetrahedron* **1992**, *48*, 10399.

(8) For recent reviews of olefin metathesis, see: (a) Grubbs, R. H.; Chang, S. *Tetrahedron* **1998**, *54*, 4413. (b) Armstrong, S. K. *J. Chem. Soc., Perkin Trans. 1* **1998**, 371.

(9) Nishiyama, T.; Woodhall, J. F.; Lawson, E. N.; Kitching, W. *J. Org. Chem.* **1989**, *54*, 2183.

(10) Lakshmipathi, P.; Rao, A. V. R. *Tetrahedron Lett.* **1997**, *38*, 2551.

(11) Schwab, P.; Grubbs, R. H.; Ziller, J. W. *J. Am. Chem. Soc.* **1996**, *118*, 100.

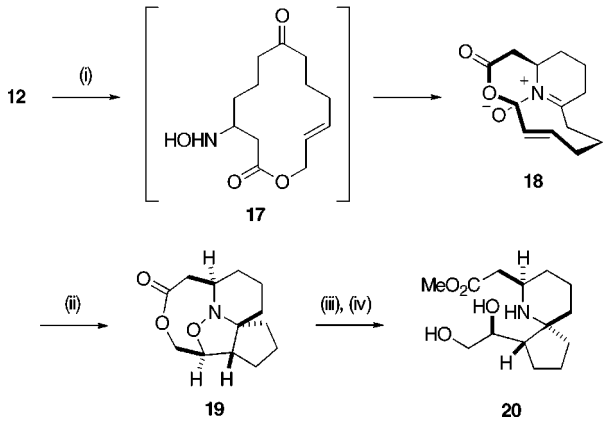
(12) Use of Grubbs' recently reported olefin metathesis catalyst, tricyclohexylphosphine[1,3-bismesityl-4,5-dihydroimidazol-2-ylidene]-benzylideneruthenium(IV) dichloride, provided no advantage in yield, see: Scholl, M.; Ding, S.; Lee, C. W.; Grubbs R. H. *Org. Lett.* **1999**, *1*, 953.

(13) For a review of the Staudinger reaction, see: Gololobov, Y. G.; Kasukhin, L. F. *Tetrahedron* **1992**, *48*, 1353.

respectively.[15] TLC analysis of the reaction mixture suggested that isomerization of the oxaziridine occurred before RCM and none of the desired compound **12** was formed. Interestingly, in a separate experiment **15** was converted to **16** in 95% yield (E:Z = 6:1) by the action of just 5 mol % of **10**. [16]

Exposure of **12** to *p*-toluenesulfonic acid in aqueous MeOH resulted in simultaneous hydrolysis of the ethylene ketal and the oxaziridine to give transiently the keto hydroxylamine **17** (Scheme 4). The latter underwent spontaneous intramolecular condensation to produce nitrone **18** as a 4:1 mixture of *E* and *Z* isomers. It proved possible at this stage to remove the minor *Z* isomer by careful column chromatography. Conformational analysis of nitrone **18** indicates that the macrocycle is too small to allow the nitrone oxygen to pass through the ring, and hence transannular cycloaddition should occur preferentially at only the rear face of the double bond as shown in **18**. In fact, a solution of **18** in toluene heated to reflux afforded a single crystalline product, X-ray analysis of which revealed its structure to be

Scheme 4. Transannular Cycloaddition of Nitrone **18**



(i) *p*-TsOH•H_2O, MeOH–H_2O (5:1), Δ, 70%; (ii) Toluene, Δ, 64%; (iii) K_2CO_3, MeOH, Δ, 88%; (iv) SmI_2, THF, rt, 64%.

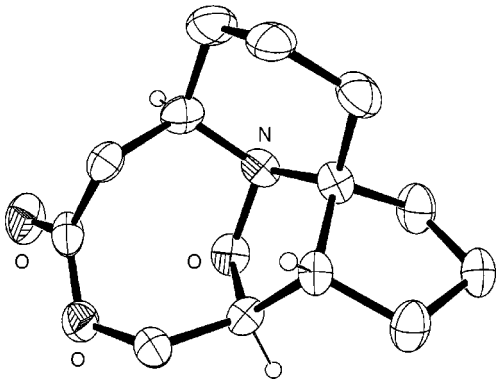


Figure 1. ORTEP diagram for **19**. Ellipsoids are drawn at the 30% probability level.

19 (Figure 1). As expected, the relative configuration of the three new stereogenic carbons in this tetracyclic isoxazolidine emanates from the single stereogenic center in **18** along with the trans geometry of the alkene and affirms the proposition that good stereocontrol can be realized in transannular dipolar cycloadditions of this type.

Finally, base-catalyzed methanolysis of lactone **19** followed by reductive cleavage of the isoxazolidine with samarium diiodide[17] gave the dihydroxy amino ester **20** representing the azaspirocyclic core of pinnaic acid (**1**). This demonstration of TANCA not only opens a practical route to **1** but should provide stereocontrolled access to a wide variety of heterocycles. Further development of this new principle of synthesis will be reported in due course.

Acknowledgment. Financial support was provided by the National Institutes of Health (GM58889).

Supporting Information Available: Detailed experimental procedures and characterization data for all new compounds. X-ray crystallographic data for **19**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(14) A similar transformation sequence has been reported by Holmes and co-workers: Holmes, A. B.; Smith, A. L.; Williams, S. F.; Hughes, L. R.; Lidert, C.; Swithenbank, C. *J. Org. Chem.* **1991**, *56*, 1393.

(15) The isomerization of oxaziridines to amides is usually base catalyzed: Davis, F. A.; Sheppard, A. C. *Tetrahedron* **1989**, *45*, 5703.

(16) For macrocyclic RCM to yield other 14-membered lactones, see: (a) Fürstner, A.; Langemann, K. *J. Org. Chem.* **1996**, *61*, 3942. (b) Lee, C. W.; Grubbs, R. H. *Org. Lett.* **2000**, *2*, 2145.

(17) Keck, G. E.; Wager, T. T.; McHardy, S. F. *Tetrahedron* **1999**, *55*, 11755.